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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,349	CARTIER ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/9/01, 2/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the reply filed on February 8, 2006 is acknowledged. The traversal is on the ground(s) that the teachings of the cited reference do not teach the special technical feature of the claims as amended. As amended, the present claims share the common feature of having, in one ml dose of the claimed vaccine, less than 1.2 mg of an aluminum salt, antigens from poliovirus, diphtheria (4 Lf/ml), tetanus (10 Lf/ml), and pertussis. It is noted that the teachings of the WO 93/24148 reference indicates that, with the addition of pertussis antigens, the resulting vaccine formulation would have an additional 150 mg of aluminum per .5 ml dose. Thus, the reference does not teach a formulation according to the claimed invention. Because the reference does not teach each of the common technical features of the claims, unity of invention is found, and the requirement for restriction between Groups I and II is withdrawn.

2. Claims 1, 4, and 9-12 are pending in the application.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on October 9, 2001 and on February 8, 2006 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements been considered by the examiner.

4. It is noted that the sole reference cited in the February 2006 IDS was previously cited in the October 2001 IDS. This reference has therefore been crossed out in the later IDS as it was already made of record and considered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 4, and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is drawn to a multivalent vaccine composition described as a "booster vaccine."

Claim 11 is drawn to a method of immunizing an individual using the formulation of claim 1 wherein the formulation is administered in three doses, the first two doses being 1 to 2 months apart, and the third dose from 6-12 months after the second dose. However, the schedule of administration described by claim 11 is described in the application as being a schedule used for primary immunization.

Because claim 1 indicates that the vaccine is a booster vaccine, and claim 11 appears to read on a primary immunization method, it is unclear what the "booster vaccine" language of claim 1 is intended to describe.

Clarification is required.

It is suggested that the "booster vaccine" limitation is deleted from the claims as the language does not appear to provide more than one potential use of the claimed formulation.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Florent et al. (WO 98/19702) in view of the teachings of Fahim et al. (WO 98/00167) (both of record in the October 2001 IDS). Claim 1 is drawn to a vaccine formulation of 1 ml comprising the following components:

less than 1.2 mg of an aluminum salt,

poliovirus and Bordetella pertussis antigens,

4 Lf of Corynebacterium diphtheria antigens, and

10 Lf of Clostridium tetani antigens.

The claim indicates that the vaccine is to be used as a booster vaccine. Claim 10 is drawn to a method of immunizing a human against at least poliovirus, diphtheria, and tetanus through the administration of the vaccine. Claim 12 limits claim 10 to embodiments wherein the vaccine is administered either intramuscularly or subcutaneously in one or two doses. It is noted that the method of claim 12 is indicated in the application as being the mode of administration used where the vaccine is used as a booster vaccine. Page 15.

Florent teaches a .5 ml vaccine formulation comprising B pertussis antigens, 2 Lf of diphtheria antigens, and 5 Lf tetanus antigens. Claims 1 and 2. The reference teaches that these lower dosage formulations are equally effective as, but have lower reactogenicity in comparison

to, other higher dosage formulations. Pages 1-2. Because the reference is teaching a .5 ml dose vaccine (half the volume of the presently claimed composition), and provides diphtheria and tetanus antigens in half the amount of the present claims, the composition of the reference is equivalent to that of the presently claimed 1 ml dose. The reference also teaches that the vaccine may be used as a booster vaccine. Page 2, lines 7-12. However, the reference does not teach the adjuvant limitations of the present claims.

What Florent does teach is that the disclosed lower doses of diphtheria, pertussis, and tetanus antigens may be used in known DTP combination vaccines without loss of immunogenicity. Pages 1-2. Thus, the reference suggests the substitution of the low dose DTP formulation provides therein for the higher DTP doses provided in other formulations.

Fahim teaches a combination vaccine comprising pertussis, diphtheria, and tetanus antigens in the higher doses referred to on page 1 of the Florent reference. Pages 15 (lines 16-23) and 109 (claim 16). The composition additionally comprising poliovirus antigens, and aluminum phosphate in concentration of 1.5 μg/.5 ml (3 μg/ml- which is a less than 1.2 mg/ml). In view of the teachings of Florent as described above, it would have been obvious to those of ordinary skill in the art to substitute the low dose DTP formulation for higher doses of the DTP formulation in Fahim, resulting in a vaccine formulation according to the claimed invention. The motivation for the substitution in the make combination vaccines the cause fewer reactions that higher dose vaccines.

Thus, the Florent reference indicates that the low dose formulation described therein is safe and effective for human use, and suggests the use of this formulation instead of the higher doses used in other combination vaccines. Those of ordinary skill in the art would therefore have

had a reasonable expectation of success in the substitution of the lower doses of diphtheria and tetanus disclosed therein for the higher doses in vaccine such as are disclosed in Fahim. The combined teachings of Florent and Fahim therefor render the claimed inventions obvious.

In addition, Fahim also teaches that the vaccines disclosed therein may be administered intramuscularly or subcutaneously. Page 37. Further, the reference also teaches that the regimes for both the initial and booster administrations may vary, and may include an initial administration followed by subsequent administrations. Page 38. Thus, the reference indicates that the indicated multivalent vaccines may be used as booster vaccines, and that such booster vaccines may be administered in one or more administrations. It is noted that, in art, it was recognized that DTP multivalent vaccines could be administered in regimes wherein multiple doses were administered from 1, 2, or more months apart. See e.g., Galazka et al., Vaccine 14: 845-57 (of record in the October 2001 IDS- teaching on page 847 a schedule of administration including multiple doses separated by at least 1 month); and Swartz et al., Develop Biol Stand 65: 159-66 at page 160. In view of these teachings by Fahim, and the understanding the art that multiple doses in a regime may be administered in time periods of 1 or more months apart, the regimes described by claim 12 would have been obvious to those of ordinary skill in the art.

9. Claims 1, 4, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Florent et al. (WO 98/19702), in light of the teachings of Petre et al. (WO 3/24148), and in view of the teachings of Gupta et al. (Vaccine 13: 1263-76) and Scheifele et al (Immunol Infect Dis 5: 73-77)- (all of which references were made of record in the October 2001 IDS).

Claims 1 and 10 have been described above. Claim 4 additionally requires the presence of one of a hepatitis A or B vaccine.

The teachings of Florent have been described in part above. The reference teaches a multivalent vaccine composition that has, as required by the claims, 4 Lf of diphtheria and 10 LF of tetanus antigens per 1 ml dose. The reference also teaches the combination of these formulations with additional antigens, including those from hepatitis A, hepatitis B, and polio. Claims 4 and 6. Additionally, Florent indicates that the vaccine may be used as a booster vaccine in previously immunized individuals. Page 2, lines 7-12. In the examples provided by Florent, the reference teaches that the exemplary vaccines comprise an adjuvant, and identifies aluminum phosphate or hydroxide as adjuvants that may be used. Claims 1 (line 2), and claims 7 and 8. On page 6 (lines 8-10), the reference states that the aluminum adjuvants present in the examples were provided in the amounts described in the Petre publication.

Petre teaches compositions comprising cellular B. pertussis, diphtheria, and tetanus antigens with .45 mg/.5 ml (.9 mg/ml) of aluminum adjuvant. Page 10 (Example 2). However, the reference also indicates that other antigens added to the composition would also be formulated with an adjuvant, with a cumulative presence of greater than 1.2 mg/ml where each of the antigens required in claim 1 is present. See e.g., page 4 (lines 6-9), and page 5 (lines 21-24). Thus, neither reference specifically teaches formulations with each of the antigens identified in claim 1, wherein the total aluminum (measured by the aluminum atom) present in the formulation is less than 1.2 mg/ml.

However, while the teachings of Petre are limited to the use of aluminum salt adjuvants, Florent indicates that other adjuvants may be used as substitutes for aluminum adjuvants. Page 5,

lines 25-27 (teaching that the aluminum adjuvants are preferred, but indicating that any suitable adjuvant may be used). Thus, while the Florent reference does not specifically teach the use of lower doses of aluminum, it does indicate that other adjuvants than aluminum may be used.

The teachings of Gupta indicate that aluminum adjuvants sometimes induce local reactions when administered. See e.g., Gupta, page 1269 right column. Gupta additionally teaches that other adjuvants, such as liposomes, provide immunogenic results on par with those achieved using aluminum adjuvants. Page 1271, right column (second full paragraph in section entitled "Liposomes"). These results were seen using both tetanus and diphtheria antigens. From these teachings, in combination with the suggestion in Florent that other adjuvants than aluminum may be used, it would have been obvious to those of ordinary skill in the art to use such other adjuvants in the place of aluminum. Those of ordinary skill in the art would therefore have been motivated to use such other adjuvants so as to further reduce the reactogenicity of the vaccine formulations of Florent.

Those of ordinary skill in the art would have had a reasonable expectation of success in the substitution of non-aluminum adjuvants based on the indication in Florent that any suitable adjuvant may be used, and the teachings in Gupta that other adjuvants are useful in inducing immune responses against the antigens included in the multivalent vaccine disclosed by Florent (esp., the tetanus and diphtheria antigens).

Because the art renders obvious vaccine formulations where other adjuvants than aluminum are used, the art renders obvious vaccine formulations where less than 1.2 mg/ml of aluminum is present. This is because substitution of the aluminum adjuvant with such other adjuvants would result in a formulation with less than 1.2 mg/ml of aluminum. Therefore,

because the art indicates that other adjuvants than aluminum may be used in the suggested multivalent vaccine formulations, and the teachings in the art suggest the use of such other adjuvants to reduce reactogenicity of the formulation, the combined teachings of these references render the claimed inventions obvious.

10. Claims 1, 4, and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Florent in light of Petre, and in view of Gupta and Scheifele as applied to claims 1, 4, and 10 above, and further in view of Swartz et al. (Develop Biol Stand 65: 159-66). Claims 1, 4, and 10 have been described above. Claim 9 reads on a kit comprising at least 2 injectable doses of the vaccine of claim 1. As described above, claim 11 reads on the methods of claim 10 wherein the formulation is administered in three doses, the first two doses being 1 to 2 months apart, and the third dose from 6-12 months after the second dose.

The teachings of the references other than Swartz have been described above. None of the references specifies a particular dose schedule for the administration of the suggested vaccine formulation. However, the Petre reference indicates that the vaccines disclosed therein may be administered according to any "appropriate vaccination schedule." Page 5, lines 1-19. Thus, it would have been obvious to those in the art that the vaccine formulation suggested by the previously cited references may be provided in any schedule known to those of ordinary skill in the art.

Such a schedule of DTP-polio vaccine administration is disclosed in the Swartz reference. See e.g., page 160 (teaching two schedules in Table I- the second of which meets the limitations of claim 11). The reference also teaches that this schedule, the 2+1 schedule, is

satisfactory in its immune response (efficacy) and clinical morbidity (reactogenicity). It is noted that, although the reference does not specify the mode of delivery, such vaccines are recognized and in the art as being administered intramuscularly or subcutaneously. See e.g., Scheifele, page 74 (teaching intramuscular injection); and Petre et al., page 15 (Example 7, teaching subcutaneous administration). Thus, the teachings of Swartz teach a schedule of administration as described by claim 11.

The Florent reference teaches that the formulations suggested therein have not lost immunogenicity (pages 1-2) compared to the high dose vaccines such as those disclosed in Petre. In view of this, and as Petre indicates that any known schedule may be used for the vaccines disclosed therein, it would have been obvious to those of ordinary skill in the art to use such known schedules for the administration of the formulations suggested by Florent. Thus, those in the art would both have been motivated to use, and had a reasonable expectation of success in the use of, the known schedule of Swartz for the administration of the vaccine formulations suggested by the previously cited references. The cited combination of references therefore renders the method of claim 11 obvious.

Further, because the art indicates that multiple doses of the vaccine may be administered, it would have been obvious to those of ordinary skill in the art to provide the vaccines in kits comprising multiple doses thereof. Thus, the kit of claim 9 is therefore also obvious over the cited references.

11. Claims 1, 4, 9, 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Arminjon et al. (WO 99/13906- of record in the October 2001 IDS) in view of Florent (supra). The claims have been described above.

It is noted that the Arminjon reference post-dates the filing date of the foreign application EP application 98122373.8 (in the French language) to which priority is claimed. However, the Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Because no such translation has been provided, and as the Arminjon reference predates the earliest U.S. filing, the reference qualifies as prior art with a 35 U.S.C. 102(a) date.

Arminjon teaches multicomponent vaccines comprising an aluminum adjuvant. In one instance, the reference teaches a vaccine comprising diphtheria, tetanus, poliovirus, pertussis, and hepatitis B antigens, and .306 mg of aluminum in a .5 ml dose (equivalent to a dose with about .6 mg/ml of aluminum). See e.g., page 13. The reference therefore teaches a vaccine composition comprising each of the components of the vaccine of claims 1 and 4, although the vaccine varies from the claimed vaccine in the amount of the tetanus and diphtheria antigens present. The reference also teaches that the vaccines may be administered through intramuscular or subcutaneous injection. Page 14, lines 13-15. Further, the reference also indicates that the regimes by which the vaccines may be administered are variable, but that they may include an initial dose followed by subsequent administrations.

As was previously described, it was known it the art that the administration of similar vaccines may include an initial administration followed by additional administrations one or two months thereafter. See e.g., the teachings of the Galazka and Swartz as described in paragraph 8

above. Thus, based on this knowledge, and the suggestion in Arminjon that the vaccine be administered in an initial dose followed by additional doses, it would have been obvious to those of ordinary skill in the art to administer the vaccine of Arminjon with an initial dose followed by a second dose at least one month thereafter. However, Arminjon does not teach embodiments wherein the vaccine comprises tetanus and diphtheria antigens present at a dose of, respectively, 10 and 4 Lf/ml.

The teachings of Florent have been described above. As was previously described, the reference teaches a vaccine composition comprising low doses of both tetanus and diphtheria antigens corresponding to the amounts required by the rejected claims. See e.g., claim 2. Additionally, the reference also indicates that these low dose formulations may be combined with other antigens without a loss of immunogenicity (page 2, lines 4-6), and suggests the use the disclosed low antigen doses in combination vaccines disclosed by the art (e.g., page 3, lines 26-32). Based on these teachings, it would have been obvious to those of ordinary skill in the art to substitute the antigen formulation of Florent for the DTP components of the combination vaccine in Arminjon. The resulting combination vaccine would comprise the diphtheria and tetanus components of Florent (equivalent to those of the present claims) and the aluminum component of Arminjon.

The motivation for combining these teachings would have been to take advantage of the reduced reactogenicity of the reduced antigen formulation in Florent. See e.g., pages 1-2. Further, because the reference indicates that the low dose composition disclosed therein may be combined with other vaccines without a loss of immunogenicity, suggests the substitution of the low dose formulation into other known formulations, and provides a successful demonstration of

such a substitution (e.g., Examples 1 and 2, pages 6-8), those in the art would have had a reasonable expectation of success in the substitution. Thus, the combined teachings of the cited references render the claimed inventions obvious.

Conclusion

12. No claims are allowed.

13. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

Laroche et al., Infection 27: 49-56 (of record in the October 2001 IDS). This reference teaches a DTP vaccine formulation with a reduced quantity of the diphtheria toxin, and teaches that this formulation is effective as a booster vaccine in adults, and has improved safety in that it has lower toxicity than the formulations with higher diphtheria doses. Page 54. The reference is considered supportive of, and redundant to the teachings of Florent as applied above.

Feery et al., Med J Aust 1: 128-30. Like Florent, this reference also teaches that reduced amounts of diphtheria toxin are sufficient to induce a protective response against the target pathogen, at least in previously primed individuals. Page 128. Further, the reference additionally teaches the administration of booster doses of the reduced dose of diphtheria according to a schedule as described in claim 11. Page 129 (Methods section). The reference is therefore considered redundant to, but supportive of, the combination of Florent and Swartz as applied above.

Englund et al., Pediatrics, 93: 37-43. This reference teaches a number of DTP vaccines. Each of these vaccines vary from the claimed compositions (with respect to the DTP constituents) in that none of the tetanus or diphtheria antigen doses matches that of the claimed formulation. The reference teaches that these vaccines may be used as booster vaccines. The reference is considered redundant, to some extent, to the teachings of Fahim.

Aggerbeck et al., Vaccine, 14:1265-1272 (September 1996). Like the Gupta reference, this reference also teaches the substitution of aluminum adjuvants with another adjuvant.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner